REMARKS/ARGUMENTS

Claim Status/Support For Amendments

In response to the Office Action of June 16, 2003, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

No new matter has been added by the amendments to the specification.

The title of the application has been amended to more clearly indicate the invention to which the pending claims are drawn.

Several protocols in the experimental section of the detailed description have been amended to properly identify the trademark SEPHAROSE.

Sequence identification numbers have been added to the Detailed Description of the Invention section of the instant specification in order to place the application in compliance with the Sequence Rules.

The abstract has been amended to remove the legal phraseology ("said").

Claim 1 has been amended to incorporate the subject matter of canceled claim 2. Claims 2-38 have been canceled. New claims 39-46 have been added. Claims 1 and 39-46 remain pending in this application. Claim 1 (as drawn to SEQ ID NO:1 and SEQ ID NO:4) now constitutes said Group I invention. As later explained, under the heading **Request for Rejoining of Claims** (see page 12), if this

claim is deemed to be allowable, rejoinder of the remaining claims in accordance with *Ochiai* is respectfully requested.

No new matter has been added by the addition of new claims 39-46. The subject matter of new claims 39-46 corresponds to subject presented in canceled claims 3-38. The above additions to the claims also find basis in the original disclosure at page 25, line 16 to page 26, line 22. The method of new claim 39 is described in detail at pages 37-47. Page 48, lines 11-15, refers to use of various types of samples and page 39, lines 7-20, refers to different mass spectrometric techniques. Page 47, line 11, refers to practicing the claimed methods with a human patient. Pages 47-48 describe kits contemplated for use with the claimed methods. Lines 6-15 on page 48 refer particularly to the immobilizing on solid supports and labeling of components of the contemplated kits. It is clear from these specific recitations and from the description of methods utilized that the methods and types of kits recited in the newly added claims (39-46) were fully contemplated by the inventors at the time of filing and were enabled by virtue of the disclosure as originally filed.

Reference Cited in Response to Restriction Requirement

The reference cited in the Response to the Restriction Requirement filed on March 31, 2003 (Scott & Mercer, Concise Encyclopedia:Biochemistry and Molecular Biology, Third Edition,

Walter de Gruyter, Berlin, 1997, page 225) was cited specifically to support Applicants' traversal of the restriction requirement and not intended to be considered in its entirety. Thus, said reference is not cited in an IDS in accordance with 37 CFR 1.97.

Request for Rejoining of Claims

The instant application is related in claim format to several pending applications of which serial number 09/846,352 is exemplary. The biopolymer marker of serial number 09/846,352 was found to be novel and subsequently claims reading on methods and kits limited to its use were rejoined with the claims reading on the biopolymer marker under *Ochiai*. In an effort to maintain equivalent scope in all of these applications, Applicants respectfully request that the Examiner enter the new claims 39-46 in the instant application as being drawn to a non-elected invention and consider joining them (new claims 39-46) with claim 1 of the elected invention (Group I) upon the Examiner's determination that claim 1 of the elected invention is allowable, since if SEQ ID NOS: 1 and 4 are found to be novel, methods and kits limited to their use should also be found novel.

Sequence compliance

The following paragraph clarifies the use of parentheses in SEQ ID NO:2. The first (R) and last (A) amino acid residues of SEQ

ID NO:2 are shown in parentheses in the original disclosure at page 46 (line 18). When carrying out mass spectrometric procedures, it is possible to fragment a whole molecule, depending upon the enzyme used for digestion. A sequence is often predicted from these fragments but often the sequence is not identified completely. It is conventional in the art to show the missing portions of the predicted sequence in parentheses. The first and last amino acid residues of SEQ ID NO:2 are predicted residues as disclosed by the parentheses. The first and last amino acid residues of SEQ ID NO:2 are disclosed in the specification and the Sequence Listing, however the biopolymer marker peptide identified in patient sera consists of amino acid residues 2-18 of SEQ ID NO:2.

Objection to the Amendment filed on April 23, 2002

The Examiner has indicated that the amendment to the specification filed on April 23, 2002 has not been entered into the instant application because it is not in compliance with 37 CFR 1.121. Specifically, the Examiner indicates that Applicant failed to identify the location of the replacement paragraph within the specification and further failed to provide the full text of the amended paragraphs containing sequence identifiers.

The amendment to the specification (at page 46) originally filed on April 23, 2002 is filed herewith in a format in

compliance with 37 CFR 1.121. Thus, Applicants now respectfully request that the Examiner enter the amendment.

Rejection under 35 USC 101

Claims 1 and 2, as originally presented, stand rejected under 35 U.S.C. 101 because the claimed invention allegedly is directed to non-statutory subject matter. The Examiner alleges that the claims fail to include any limitations, which would distinguish the claimed polypeptide sequences from those which occur in nature.

Claim 2 has been canceled and the subject matter of claim 2 has been incorporated into amended claim 1. Claim 1 has been amended to recite an isolated biopolymer marker. As used within the instant specification (at page 20, lines 9-16), the term "isolated"is interpreted to mean "altered by the hand of man" from its natural state, for example, if it occurs in nature and it is then "isolated", it has been changed or removed from its original environment or both. A polypeptide, such as that claimed herein (SEQ ID NO:1 and SEQ ID NO:4), naturally present in a living organism is not "isolated", however the same polypetide separated from the co-existing materials of its natural state is "isolated". It is clear from the methods recited herein that the claimed polypeptide markers (SEQ ID NO:1 and SEQ ID NO:4)are obtained from samples which have been isolated from a patient's body, thus

the claimed polypeptide is "isolated" (see page 47, lines 9-20).

Accordingly, it is respectfully submitted that the Applicants have now shown that the claimed invention is drawn to patentable subject matter. Thus, Applicants respectfully request that the above-rejection under 35 U.S.C. 101 be withdrawn.

Rejection under 35 USC 112 (second paragraph)

Claims 1 and 2, as originally presented, stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner alleges that claim 1 is vague and indefinite because it is not clear whether "analyte thereof" refers to a biopolymer marker or to SEQ ID NO:1 or 4. The Examiner states that according to the instant specification, "biopolymers" are defined as "biological molecules/macromolecules" and an "analyte" is defined as "any atom and/or molecule; including their complexes and fragment ions" (page 6, lines 15-19). The Examiner alleges that the definitions of these two terms appear to be conflicting, because one would not recognize an atom as a biopolymer.

Claim 2 has been canceled and the subject matter of claim 2 has been incorporated into amended claim 1. Claim 1, as amended herein, does not recite the phrase "analyte thereof". The phrase "analyte thereof" is not recited in any of the remaining pending

claims. Furthermore, it is clear from reading amended claim 1 that SEQ ID NO:1 and SEQ ID NO:4 are the biopolymer markers.

Accordingly, applicants have now clarified the metes and bounds of the claims and respectfully request that the above-discussed rejection under 35 U.S.C. 112, second paragraph be withdrawn.

Rejection under 35 USC 112 (first paragraph)

Claims 1 and 2, as originally presented, stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was allegedly not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner alleges that the instant specification fails to provide any guidance on how to use the disclosed polypeptides of SEQ ID NO:1 or SEQ ID NO:4 or analytes thereof as a marker or indicator of any disease state, including Type II diabetes. The Examiner further asserts that there is no information disclosed in the instant specification which would provide evidence or sound scientific reasoning that a biopolymer marker (SEQ ID NO:1 or SEQ ID NO:4 or analyte thereof)is specifically associated with any particular disease state in general or with Type II diabetes in particular.

Applicants respectfully disagree with the Examiner's assertions. Claim 2 has been canceled and the subject matter has been incorporated into amended claim 1. Neither claim 1, as amended herein, nor any of the other remaining pending claims recite the term "analyte". Claim 1 has been limited to specific biopolymer marker peptides (SEQ ID NO:1 and SEQ ID NO:4) specifically diagnostic for Type II diabetes. Applicants are not required to explain the disease process in type II diabetes; applicants are only required to show that the claimed peptides are indicative of type II diabetes (see MPEP 2165.03). Applicants respectfully submit that the instant disclosure including the figures show that the claimed peptides are indicative of type II diabetes.

Applicants provide a general disclosure of the protocols and methods used to identify the claimed biopolymer marker peptides at pages 37-40 of the instant specification. Pages 40-46 of the instant specification provide specific steps and protocols one would carry out in order to identify the claimed biopolymer marker peptides. Furthermore, mass spectrometric and chromatographic techniques are well-known to those of skill in the art, thus even if specific protocols were not included within the disclosure, one of skill in the art would know how to carry out the protocols in the instant disclosure. Applicant is not required to describe what is well known in the art. A patent need not teach, and preferably

omits, what is well known in the art (see MPEP 2164.01).

Applicants clearly teach in the instant specification how the claimed peptides were determined to be diagnostic for Type II Diabetes and further set forth a protocol which can be followed to determine markers of any disease condition. For example, according to the method of the instant invention; biological samples (types of samples are listed at page 48, lines 11-15 of the instant specification) are obtained from both patients having a disease condition and healthy (normal) patients. The two groups of samples are resolved by polyacrylamide gel electrophoresis and the resulting protein bands appearing from the diseased samples are compared to the protein bands appearing from the normal samples. Bands which differ in some way (down-regulated, up-regulated. present or absent) between the samples are excised from the gel. Thus, none of the bands on either gel (figure 1 or figure 3)correspond directly to the claimed peptides. The bands represent whole proteins or groups of proteins as they are separated from the patient sample. The claimed peptides are fragments of the whole proteins excised from the gel. After excision from the gel, the proteins are then purified (from the gel) and are subjected to enzymatic digestion, chromatography and identification by mass spectrometric techniques. For example, figures 1 and 3 show that band 1 (fibronectin precursor) is strongly present in serum from normal patients (lanes 1-4 in Figure 1 and lanes 7-10 in Figure 3,

as read from the left) as compared with serum from patients having a history of Type II diabetes (lanes 5-9 of Figure 1 and lanes 2-6 of Figure 3, as from the left). The bands corresponding to bands 1 of both gels (not labeled in the figures)shown in figures 1 and 3 were excised and subjected to the above-described protocol. The claimed peptides (SEQ ID NOS: 1 and 4) were identified as fragments of the fibronectin precursor. This data supports the hypothesis of the instant inventors wherein fibronectin is fragmented during the disease process of Type II diabetes since the fragmented fibronectin is identified from the lighter bands corresponding to bands 1 of healthy patients. Since the fibronectin precursor was strongly expressed in normal patients but appeared as fragments in patients with a history of Type II diabetes, the claimed peptides are considered to be indicative of type II diabetes. Thus, applicants respectfully submit that the instant specification provides sufficient guidance on how to identify and use the claimed peptides as markers of type II diabetes.

There is no conventional control applied in the methods of the instant invention. Both samples from diseased patients and samples from healthy patients are separated by gel electrophoresis. The bands which differ between diseased and healthy samples are excised from the gel. A determination of up-regulation, down-regulation, presence or absence of the proteins

present in the bands is assessed by sample wherein they appear, for example, the claimed peptide fragments were excised from bands which appeared lighter in the diseased samples as compared with the healthy samples. This is considered to be down-regulation of the protein in the diseased state.

A Declaration Under 37 CFR 1.132 is submitted herewith in order to clarify the use of controls in the experiments disclosed in the specification.

One of skill in the art would recognize from the protocols and figures disclosed in the instant specification that the claimed biopolymer marker peptides are indicative of Type II diabetes. Thus, Applicants respectfully submit that the instant specification provides sufficient guidance on how to use the claimed biopolymer marker peptides as indicators of Type II diabetes.

The Examiner asserts that the specification fails to explain the relationship between the claimed biopolymer marker peptides and a particular disease state. Applicants respectfully disagree with the Examiner's position. On page 5, lines 12-22, states that the present inventors do not attempt to develop a reference of "normal" but rather strive to specify particular markers whose presence, absence or relative strength/concentration in disease vs. normal is diagnostic of at least one specific disease state or whose up-regulation or down-regulation is predictive of at least

one specific disease state. The relationship is observed from a comparison of disease samples to normal samples. This is a simple method of analysis that requires identification of differences in the samples of the disease state versus the samples of the non-disease state. Such simple analysis does not require "undue experimentation".

Accordingly, Applicants assert that one of ordinary skill in the art when reviewing the instant specification would recognize how to use the claimed biopolymer marker peptides (SEQ ID NO:1 and SEQ ID NO:4) as markers for indication of Type II diabetes. Thus, Applicants respectfully request that this rejection now be withdrawn.

CONCLUSION

In light of the foregoing remarks, amendments to the specification and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,

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